ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Volume 544
December 14, 1988

ANTIFUNGAL DRUGS[a]

Editor and Conference Chairman
VASSIL ST. GEORGIEV

Conference Cochairmen
HIDEYO YAMAGUCHI and C. RICHARD KINSOLVING

Session Chairs
JOHN E. BENNETT, JEROME BIRNBAUM, DAVID J. DRUTZ, MARVIN GORMAN, ARNOLD L. LENTNEK, and DINU RANE

CONTENTS

Fungal Infections and the Search for Novel Antifungal Agents: Opening Remarks. *By* VASSIL ST. GEORGIEV 1

Part I. Design, Synthesis, and Structure-Activity Relationships of Antifungal Agents

Design and Evaluation of a Systemically Active Agent, Fluconazole. *By* K. RICHARDSON, K. COOPER, M. S. MARRIOTT, M. H. TARBIT, P. F. TROKE, and P. J. WHITTLE 4

Synthesis of Antifungal Imidazoles and Triazoles. *By* MASARU OGATA 12

Synthesis and Antifungal Activity of Novel Isoxazolidine Compounds. *By* GEORGE B. MULLEN, PATRICIA A. SWIFT, GRACE A. BENNETT, THOMAS R. DECORY, DAVID M. MARYNIAK, PETER G. DORMER, and VASSIL ST. GEORGIEV ... 32

Synthesis and Structure-Activity Correlations within Allylamine Antimycotics. *By* ANTON STÜTZ 46

Structure-Activity Relationships of 2-(1*H*-Imidazol-1-yl)vinyl Ethers: Route to the New Broad-Spectrum Antifungal Agent Omoconazole. *By* L. ZIRNGIBL, J. FISCHER, U. JAHN, and K. THIELE 63

[a] All of the contributions to this volume were presented at the **First International Conference on Drug Research in Immunologic and Infectious Diseases. Antifungal Drugs: Synthesis, Preclinical and Clinical Evaluation.** The conference, which was sponsored by the New York Academy of Sciences, was held in Garden City, New York, on October 8-10, 1987.

Vibunazole and Its Enantiomers: Synthesis, Antifungal Activity, and Pharmacokinetics. *By* WOLFGANG RITTER, GRAHAM HOLMWOOD, HANS-JUERGEN AHR, KLAUS DETZER, UDO KRAATZ, MANFRED PLEMPEL, DIETRICH SCHERLING, and HANS-MARTIN SIEFERT 74

Synthesis and Structure-Activity Relationships of a Novel Antifungal Agent, ICI 195,739. *By* F. THOMAS BOYLE, DAVID J. GILMAN, MICHAEL B. GRAVESTOCK, and J. MICHAEL WARDLEWORTH 86

Pyrido[3,4-*e*]-1,2,4-triazines and Related Heterocycles as Potential Antifungal Agents. *By* M. F. REICH, P. F. FABIO, V. J. LEE, N. A. KUCK, and R. T. TESTA 101

Synthesis and Antifungal Properties of Dihydrobenzothiophene Azoles. *By* D. F. RANE, J. A. DESAI, D. LOEBENBERG, R. PARMEGIANI, and R. E. PIKE 105

Synthesis and Antifungal Properties of 14-Aminomethyl-Substituted Lanosterol Derivatives. *By* A. B. COOPER, J. J. WRIGHT, A. K. GANGULY, J. DESAI, D. LOEBENBERG, R. PARMEGIANI, and D. S. FEINGOLD 109

Part II. Structural Elucidation, Synthesis, and Antifungal Activity of Natural Products and Related Derivatives

Antifungal Substances from Marine Invertebrates. *By* NOBUHIRO FUSETANI 113

The Galbonolides: Novel, Powerful Antifungal Macrolides from *Streptomyces galbus* ssp. *eurythermus*. *By* HANS ACHENBACH, ANDREAS MÜHLENFELD, URSULA FAUTH, and HANS ZÄHNER 128

Antifungal Proteins from Plants. *By* WALDEN K. ROBERTS, BRIDGET E. LAUE, and CLAUDE P. SELITRENNIKOFF 141

Synthesis and Evaluation of LY121019, a Member of a Series of Semisynthetic Analogues of the Antifungal Lipopeptide Echinocandin B. *By* M. DEBONO, B. J. ABBOTT, J. R. TURNER, L. C. HOWARD, R. S. GORDEE, A. S. HUNT, M. BARNHART, R. M. MOLLOY, K. E. WILLARD, D. FUKUDA, T. F. BUTLER, and D. J. ZECKNER 152

Amphotericin B: Synthesis of Its Aglycone (Amphoteronolide B) and Degradation. *By* SATORU MASAMUNE 168

Hydroxamic Acid Antimycotic Antibiotics: A New Group of Antibiotics. *By* YOSHIO INOUYE, HIROMASA OKADA, and SHOSHIRO NAKAMURA 180

L-660,631, a New Antifungal Agent. *By* A. J. KEMPF, O. D. HENSENS, R. E. SCHWARTZ, R. S. SYKES, K. E. WILSON, C. F. WICHMANN, D. L. ZINK, L. ZITANO, and S. MOCHALES 183

Novel Antifungal Antibiotic BMY-28567: Structural Study and Biological Activities. *By* TOSHIKAZU OKI, KYOICHIRO SAITOH, KOZO TOMATSU, KOJI TOMITA, MASATAKA KONISHI, and HIROSHI KAWAGUCHI 184

RI-331, a New Antifungal Antibiotic. *By* HIDEYO YAMAGUCHI, KATSUHISA UCHIDA, TAMIO HIRATANI, TAKATOSHI NAGATE, NAOHARU WATANABE, and SADATOSHI OMURA..... 188

Part III. Biochemical Studies and Mechanism of Action of Antifungal Agents

Mode of Action Studies: Basis for the Search of New Antifungal Drugs. *By* HUGO VANDEN BOSSCHE, PATRICK MARICHAL, JOS GORRENS, HUGO GEERTS, and PAUL A. J. JANSSEN..... 191

Mechanism of Action and Biochemical Selectivity of Allylamine Antimycotic Agents. *By* NEIL S. RYDER..... 208

Mode of Action of Morpholine Derivatives. *By* ANNEMARIE POLAK 221

Mode of Action of L-660,631 in *Candida albicans*. *By* JANET C. ONISHI, GEORGE K. ABRUZZO, ROBERT A. FROMTLING, GEORGE M. GARRITY, JAMES A. MILLIGAN, BARBARA A. PELAK, and WALTER ROZDILSKY..... 229

Mode of Action of β-Lactone 1233A in *Candida albicans*. *By* JANET C. ONISHI, GEORGE K. ABRUZZO, ROBERT A. FROMTLING, GEORGE M. GARRITY, JAMES A. MILLIGAN, BARBARA A. PELAK, WALTER ROZDILSKY, and BARBARA WEISSBERGER 230

Biochemical Studies with a Novel Antifungal Agent, ICI 195,739. *By* KEITH BARRETT-BEE, JOYCE LEES, PHILIP PINDER, JULIE CAMPBELL, and LORRAINE NEWBOULT 231

Drug Resistance in *Candida albicans* and *Candida glabrata*. *By* DAVID KERRIDGE, MARCO FASOLI, and FRANCES J. WAYMAN..... 245

Isolation and Characterization of Fluoropyrimidine-Resistant Mutants in Two *Candida* Species. *By* MARCO FASOLI and DAVID KERRIDGE 260

Part IV. Preclinical Evaluation of Antifungal Agents

Role of Animal and Human Pharmacology in Antifungal Drug Design. *By* GEERT CAUWENBERGH and JAN VAN CUTSEM 264

Use of Chemiluminescence to Evaluate the Influence of Antifungal Agents on Immune Cell Function. *By* ROBERT A. FROMTLING, GEORGE K. ABRUZZO, TRACY A. TURNBULL, DAVID M. GILTINAN, and THOMAS P. CAPIZZI 270

In Vitro Potency and *in Vivo* Activity of Azoles. *By* PETER F. TROKE, MICHAEL S. MARRIOTT, KENNETH RICHARDSON, and MICHAEL H. TARBIT 284

Anti-*Candida* Activity and Toxicology of LY121019, a Novel Semisynthetic Polypeptide Antifungal Antibiotic. *By* ROBERT S. GORDEE, DOUGLAS J. ZECKNER, LEONARD C. HOWARD, WILLIAM E. ALBORN, JR., and MANUEL DEBONO 294

Activity of ICI 195,739—a Novel, Orally Active Bistriazole—in Rodent Models of Fungal and Protozoal Infections. *By* JOHN F. RYLEY, SANDRA MCGREGOR, and ROBERT G. WILSON 310

Evaluation of Fungicidal Action *in Vitro* and in a Skin Model Considering the Influence of Penetration Kinetics of Various Standard Antimycotics. *By* H. HÄNEL, W. RAETHER, and W. DITTMAR 329

Sterol Biosynthesis Inhibitors: Secondary Effects and Enhanced *in Vivo* Efficacy. *By* DIETER BERG, MANFRED PLEMPEL, KARL-HEINZ BÜCHEL, GRAHAM HOLMWOOD, and KLAUS STROECH 338

Activity of Triazole Derivatives against *Pityrosporum orbiculare in Vitro* and *in Vivo*. *By* JAN FAERGEMANN 348

Direct Fungicidal Action of Tioconazole. *By* WILLIAM H. BEGGS ... 354

Synergistic Effects of Ketoconazole and SF-86327 on the Proliferation of Epimastigotes and Amastigotes of *Trypanosoma (Schizotrypanum) cruzi*. *By* JULIO A. URBINA, KEYLA LAZARDI, GISELA LARRALDE, TANIA AGUIRRE, MARTA M. PIRAS, and ROMANO PIRAS 357

Substituted 5-Phenoxyalkyl-3-phenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidines: Antifungal Activity and Structure-Activity Relationship Studies. *By* GEORGE B. MULLEN, DAVID M. MARYNIAK, PATRICIA A. SWIFT, STANLEY D. ALLEN, JEFFREY T. MITCHELL, C. RICHARD KINSOLVING, and VASSIL ST. GEORGIEV 359

In Vitro Antifungal Activity of Novel Substituted 3,5-Diphenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine Derivatives. *By* THOMAS R. DECORY, GEORGE B. MULLEN, JEFFREY T. MITCHELL, STANLEY D. ALLEN, C. RICHARD KINSOLVING, and VASSIL ST. GEORGIEV 363

cis-3-(Substituted phenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methyl-5-{[(substituted phenyl)thio(or amino)]methyl}isoxazolidines: *In Vitro* Antifungal Activity and Structure-Activity Relationships. *By* THOMAS R. DECORY, PATRICIA A. SWIFT, GEORGE B.

MULLEN, JEFFREY T. MITCHELL, STANLEY D. ALLEN, C. RICHARD KINSOLVING, and VASSIL ST. GEORGIEV 366

3-(Substituted phenyl)-3-(1*H*-1,2,4-triazol-1-ylmethyl)-2-methyl-5-[(substituted phenoxy)methyl]isoxazolidine Derivatives: Structure-Activity Relationships. *By* GRACE A. BENNETT, PATRICIA A. SWIFT, GEORGE B. MULLEN, STANLEY D. ALLEN, JEFFREY T. MITCHELL, C. RICHARD KINSOLVING, and VASSIL ST. GEORGIEV 369

cis-5-Alkoxyalkyl-3-phenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine Derivatives. *By* DAVID M. MARYNIAK, GEORGE B. MULLEN, JEFFREY T. MITCHELL, STANLEY D. ALLEN, C. RICHARD KINSOLVING, and VASSIL ST. GEORGIEV 373

In Vitro Antifungal Activity of Novel Substituted 3,5-Diphenyl-3-(1*H*-1,2,4-triazol-1-ylmethyl)-2-methylisoxazolidine Derivatives. *By* GRACE A. BENNETT, PATRICIA A. SWIFT, GEORGE B. MULLEN, JEFFREY T. MITCHELL, STANLEY D. ALLEN, C. RICHARD KINSOLVING, and VASSIL ST. GEORGIEV 375

In Vitro Antifungal Activity and Structure-Activity Relationship Studies of Novel *cis*-5-Acyloxyalkyl-3-phenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine Derivatives. *By* DAVID M. MARYNIAK, GEORGE B. MULLEN, STANLEY D. ALLEN, JEFFREY T. MITCHELL, C. RICHARD KINSOLVING, and VASSIL ST. GEORGIEV 378

cis-5-Alkyl(or alkenyl)-3-phenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine Derivatives: *In Vitro* Antifungal Activity and Structure-Activity Relationships. *By* PATRICIA A. SWIFT, GRACE A. BENNETT, GEORGE B. MULLEN, JEFFREY T. MITCHELL, STANLEY D. ALLEN, C. RICHARD KINSOLVING, and VASSIL ST. GEORGIEV 381

Novel 5-Phenyl(or phenoxyalkyl)-3-(2-furanyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidines: *In Vitro* Antifungal Activity. *By* GRACE A. BENNETT, GEORGE B. MULLEN, JEFFREY T. MITCHELL, STANLEY D. ALLEN, C. RICHARD KINSOLVING, and VASSIL ST. GEORGIEV 384

Comparisons of Ketoconazole, PR 969-566, PR 967-234, and PR 967-248 as Antifungals *in Vitro* and in the Rat Model of Candidal Vaginitis based on Efficacy/Safety Profiles. *By* GENE C. PALMER, J. MARK ORDY, ROY D. SIMMONS, JAMES C. STRAND, GEORGE B. MULLEN, C. RICHARD KINSOLVING, VASSIL ST. GEORGIEV, and STANLEY D. ALLEN 387

In Vitro Activity of Novel 5-(Phenyl or phenoxyalkyl)-3-(2-thienyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidines. *By* GEORGE B. MULLEN, JEFFREY T. MITCHELL, STANLEY D. ALLEN, and VASSIL ST. GEORGIEV 392

In Vitro Activity of Novel 5-Carbonyl Derivatives of 3-Phenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidines. *By* GRACE A. BENNETT, GEORGE B. MULLEN, THOMAS R. DECORY, STANLEY D. ALLEN, JEFFREY T. MITCHELL, and VASSIL ST. GEORGIEV 396

In Vitro Activity of Novel *cis*-5-Substituted-3-(2-naphthalenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine Derivatives. *By* GRACE A. BENNETT, GEORGE B. MULLEN, STANLEY D. ALLEN, JEFFREY T. MITCHELL, and VASSIL ST. GEORGIEV 400

Enhancement of Phagocytosis and Intracellular Killing of *Candida albicans* by Human Neutrophils in the Presence of a Morpholine Antifungal Derivative, Ro 14-4767. *By* M. D. RICHARDSON and C. A. GRAY 403

Antifungal Chemotherapy with Oral Amphotericin B. *By* HIDEYO YAMAGUCHI, KATSUHISA UCHIDA, AKIO URABE, and FUMIMARO TAKAKU 406

Interferon Protects Mice against an Extracellular Infection of *Aspergillus fumigatus*. *By* R. N. TANDON, A.-R. FEUILLETTE, G. MAHOUY, G. BADILLET, R. M. FRIEDMAN, and R. K. MAHESHWARI 409

Inhibition of *Candida* Species with a Eugenol-Thymol Iodide Mixture. *By* WILLIAM R. HODGE and CIPRIANO RODAS 412

Part V. Pharmacokinetics of Antifungal Agents

Pharmacokinetics of Antimycotics with Emphasis on Local Treatment. *By* ULRICH TÄUBER 414

Steady State Parenteral Kinetics of Fluconazole in Man. *By* G. FOULDS, C. WAJSZCZUK, D. J. WEIDLER, D. C. GARG, and P. GIBSON 427

Part VI. Clinical Evaluation of Antifungal Drugs

Fungal Infections in Cancer Patients. *By* GERALD P. BODEY 431

Life-Threatening Opportunistic Fungal Infection in Patients with the Acquired Immunodeficiency Syndrome. *By* DONALD ARMSTRONG 443

Treatment of Mycoses with Itraconazole. *By* RICHARD M. TUCKER, PAUL L. WILLIAMS, EDUARDO G. ARATHOON, and DAVID A. STEVENS 451

Chronic Mucocutaneous Candidiasis: Antibiotic and Immunologic Therapy. *By* CHARLES H. KIRKPATRICK 471

Treatment of Coccidioidomycosis. *By* JOHN R. GRAYBILL 481

Ketoconazole Treatment of Coccidioidal Meningitis. *By* JOHN R. GRAYBILL, DAVID A. STEVENS, JOHN N. GALGIANI, ALAN M. SUGAR, PHILIP C. CRAVEN, CLARK GREGG, MILTON HUPPERT, GRETCHEN CLOUD, and WILLIAM E. DISMUKES.... 488

Azole Derivatives in the Treatment of Paracoccidioidomycosis. *By* RICARDO NEGRONI 497

Treatment of Chromoblastomycosis with Itraconazole. *By* ANGELA RESTREPO, AURELIO GONZALEZ, IVAN GOMEZ, MYRTHA ARANGO, and CATALINA DE BEDOUT 504

Treatment of Fungal Infections with Semisynthetic Derivatives of Amphotericin B. *By* PAUL D. HOEPRICH, NEIL M. FLYNN, MILDRED M. KAWACHI, KENNETH K. LEE, RUTH M. LAWRENCE, LARRY K. HEATH, and CARL P. SCHAFFNER 517

Pathogenesis and Epidemiology of Vulvovaginal Candidiasis. *By* JACK D. SOBEL..... 547

Prophylactic Use of Clotrimazole in Recurrent Vaginal Candidosis. *By* T. E. C. BUSHELL, E. G. V. EVANS, P. A. LLEWELLYN, J. D. MEADEN, J. D. MILNE, and D. W. WARNOCK..... 558

Single-Dose Oral Fluconazole in the Treatment of Vaginal Candidosis. *By* KEITH W. BRAMMER and JOSEPH M. FECZKO 561

Fluconazole for the Treatment of Fungal Diseases in Immunosuppressed Patients. *By* B. DUPONT and E. DROUHET 564

Parenteral 5-Fluorocytosine in the Therapy of Systemic Mycoses. *By* FRANCIS A. MINA, SCOTT J. HOPKINS, and BONNIE RICHELO..... 571

Serodiagnosis of Invasive Candidiasis. *By* LOWELL S. YOUNG and PAUL R. STEVENS 575

New Oral Treatments for Dermatophytosis. *By* RODERICK J. HAY.. 580

Topical Treatment of Onychomycosis Using Bifonazole 1% Urea/40% Paste. *By* D. T. ROBERTS, R. J. HAY, V. R. DOHERTY, M. D. RICHARDSON, and Y. M. CLAYTON 586

Correlations between Two-Feet-One-Hand Dermatophytosis, Palmar Sweating, and Handedness. *By* S. BENDER, M. WILSON, and Y. LYNFIELD..... 588

Part VII. Drug Delivery Systems of Antifungal Drugs

Liposomes as Carriers for Antifungal Drugs. *By* GABRIEL LOPEZ-BERESTEIN 590

Amphotericin B Encapsulated in Liposomes Administered to Cancer Patients. *By* F. MEUNIER, J. P. SCULIER, A. COUNE,

C. BRASSINNE, C. HEYMAN, C. LADURON, N. COLLETTE, C. HOLLAERT, D. BRON, and J. KLASTERSKY..... 598

Index of Contributors..... 611

Financial assistance was received from:

- American Cyanamid Company (Lederle Laboratories)
- Bausch and Lomb, Inc.
- Bayer AG
- Bristol-Myers Company/Pharmaceutical Research and Development Division
- Burroughs Wellcome Co.
- Eastman Kodak Company/Pharmaceuticals Division
- Hoechst-Roussel Pharmaceuticals, Inc., USA
- Imperial Chemical Industries PLC/Pharmaceuticals Division
- Janssen Pharmaceutica
- Lilly Research Laboratories/A Division of Eli Lilly and Company
- Merck, Sharp & Dohme Research Laboratories
- National Institute of Allergy and Infectious Diseases—National Institutes of Health
- Pennwalt Corporation/Pharmaceutical Division
- Pfizer Central Research, UK
- Pharma Forschung, Hoechst AG
- Roerig/A Division of Pfizer Pharmaceuticals
- Schering Corporation
- Shionogi Research Laboratories/Shionogi & Co., Ltd.
- SmithKline Beckman Corporation
- E. R. Squibb & Sons
- Verkauf Pharma/ZPM/Hoechst AG

The New York Academy of Sciences believes it has a responsibility to provide an open forum for discussion of scientific questions. The positions taken by the authors of the papers that make up this *Annal* are their own and not necessarily those of the Academy. The Academy has no intent to influence legislation by providing such forums.